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SOME EFFECTS OF LOUSE-BORNE RELAPSING FEVER ON
THE FUNCTION OF THE HEART

By

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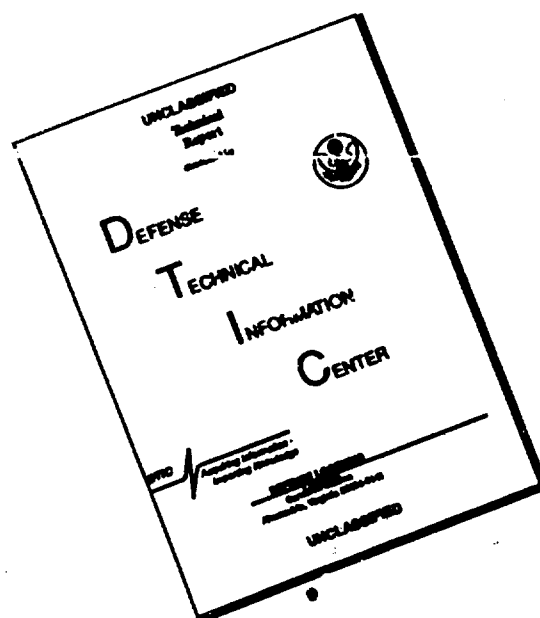
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Some Effects of Louse-Borne Relapsing Fever on the Function of the Heart

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Clinical, electrocardiographic and hemodynamic studies were made in thirty-one patients with louse-borne relapsing fever in Ethiopia; more detailed physiologic studies were made in a further nineteen patients. Evidence of an abnormal myocardium was obtained and transient acute cor pulmonale was found to occur after the reaction to treatment.

No simple correlation could be established between clinical signs and electrocardiographic and hemodynamic evidence of myocardial damage. A statistically significant correlation was found between prolonged QT_c and relative acidemia before treatment and between T wave abnormalities and hypocapnia during the chill phase of the febrile reaction following treatment.

Louse-borne relapsing fever, an endemic disease in the highlands of Ethiopia, has been known to affect the heart both from clinical [1,2] and pathologic [3,4] studies; although myocarditis has been seen at necropsy, most emphasis has been given to endocarditis.

When spirochetes of *Borrelia recurrentis* disappear from the blood after treatment with tetracycline, there is a brisk arterial pressor response, tachypnea, tachycardia and an increase in body temperature [5]. After this reaction to treatment some patients have a high central venous pressure, which may be lowered by the administration of digoxin, a gallop rhythm and a prolonged QT_c interval in the electrocardiogram [6]. Although spirochetes are cleared from the peripheral blood by a curative dose of penicillin or tetracycline, some patients die suddenly on the first and second days of treatment. We wondered whether these early deaths could be related to the histologic evidence of myocarditis and the clinical signs of an abnormal myocardium. We therefore studied the function of the heart in more detail; we were also able to investigate the relationship between changes in blood gas tensions and acid-base balance and electrocardiographic patterns. The results of these studies, and fresh evidence about the effect of Ethiopian louse-borne relapsing fever on the heart, are given.

PATIENTS AND METHODS

Fifty patients with louse-borne relapsing fever were studied. They were part of a larger series reported elsewhere [7]. The diagnosis was made by finding spirochetes of *B. recurrentis* in the peripheral blood. Every patient was treated with tetracycline, 250 mg by intravenous injection.

Of these fifty patients, thirty-one (group I) were studied simply at the bedside with techniques described previously [5]. A standard 12-lead electrocardiogram was taken at least once in every patient, using a Cambridge Transrite III machine. The records were examined by one observer and verified by a second. The Minnesota code was not used. The mean frontal plane QRS axis was determined in the conventional way.

The remaining nineteen patients (group II) were studied in greater detail by methods described fully elsewhere [8]. On admission, blood was sampled for measurement of serum electrolytes and blood urea nitrogen by spectrophotometer. Rectal temperature (T_r) was measured continuously with an electronic thermometer (McDonnell, London, Type MC3). Brachial artery (PE 60) and right heart (PE 160) polyethylene catheters

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were introduced using the Seldinger percutaneous technic and were connected to saline-filled manometers. The position of the tip of the cardiac catheter was judged by observing the height of the saline column and the characteristics of the transmitted pulsation. No portable x-ray or screening facilities were available, but in five patients the catheter was advanced into the pulmonary artery. Mean pressures in the brachial artery (\bar{P}_{br}) and right side of the heart (right ventricle \bar{P}_{rv} , or pulmonary artery \bar{P}_{pa}) were read at fifteen minute intervals from the saline manometers using the sternal angle (at +5 mm Hg relative to mean atrial pressure) as reference point with the patients lying supine.

Before treatment and during the reaction after tetracycline injection, arterial blood was drawn anaerobically into heparinized syringes and was analyzed immediately for oxygen tension (P_{aO_2}), carbon dioxide tension (P_{aCO_2}) and pH using Radiometer electrodes. pH values were converted to hydrogen ion concentration (H^+).

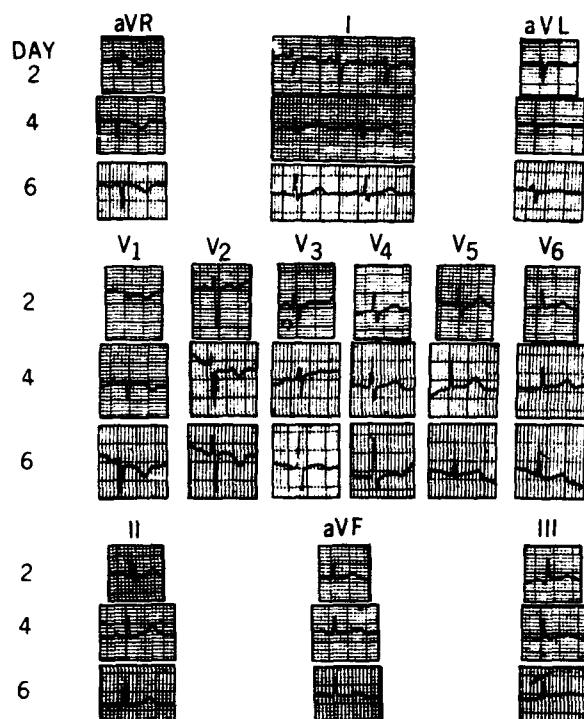


Figure 1. Electrocardiogram from a twenty-four year old man who died from louse-borne relapsing fever. Marked prolongation of the QT_c interval is illustrated.

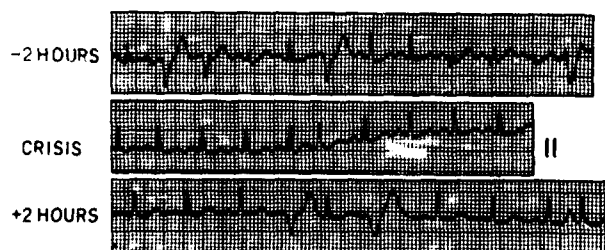


Figure 2. Electrocardiogram from a patient with louse-borne relapsing fever illustrating the occurrence of multiple ventricular ectopic beats before, during and after the reaction to treatment (crisis).

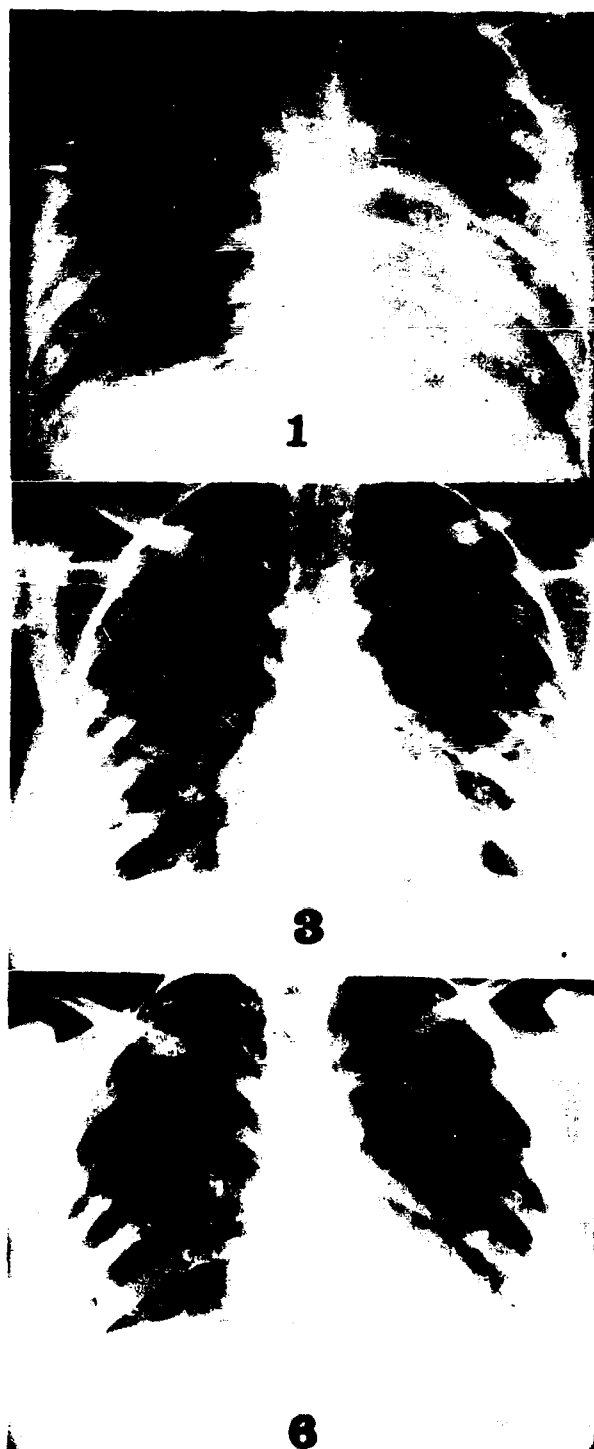


Figure 3. Serial posteroanterior chest roentgenograms taken on the first, third and sixth (1, 3 and 6) days after treatment from a patient with louse-borne relapsing fever illustrating decrease in cardiac size and disappearance of pulmonary edema between the second and sixth days after treatment.

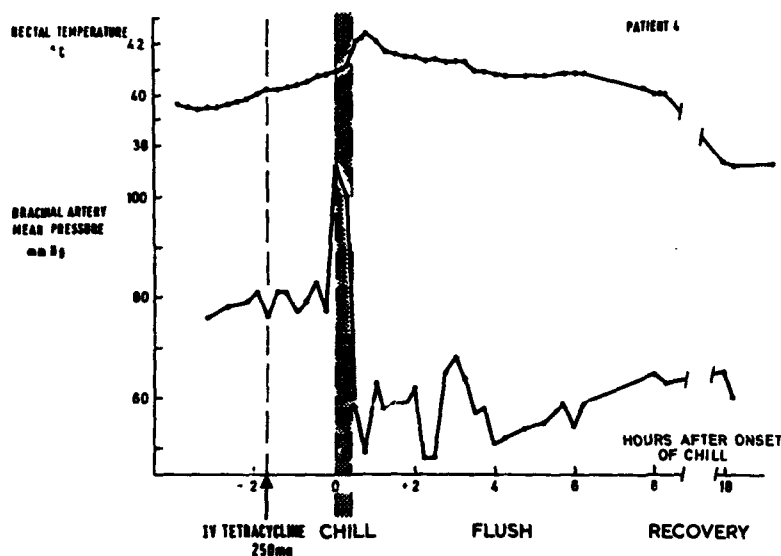


Figure 4. Rectal temperature (T_R) and brachial arterial mean pressure (\bar{P}_{RA}) in a patient with louse-borne relapsing fever illustrate the fall in systemic arterial pressure after the febrile reaction to treatment. The hatched area represents the duration of rigors.

The 95 per cent confidence limits for the estimations in this laboratory are $P_{O_2} \pm 0.74$ mm Hg, $P_{CO_2} \pm 0.52$ mm Hg and $pH \pm 0.008$ units. These values were corrected from the temperatures at which they were measured (37°C) to the body temperature (T_R) when blood was sampled [8].

A 12-lead electrocardiogram was taken at the time blood was sampled before treatment, during the rigors at the height of the febrile reaction, during the hypotensive (flush) phase which followed, on the next day and, in a few patients, at intervals during the next week.

Whenever possible, standard posteroanterior chest roentgeno-

grams were taken before treatment, on the day after treatment and subsequently when required.

STATISTICAL METHODS

In seventeen of the nineteen patients in group II, the correlation of five of the most important physiologic variables (T_R , heart rate, P_{aCO_2} , P_{aO_2} , and H^+a) individually with each of the three most common electrocardiographic abnormalities (abnormal T waves, S-T segment depression and prolonged QT_c interval) before treatment and during the rigors was tested for statistical significance as follows. The patients were divided into two groups according to the presence or absence of each of these three electrocardiographic abnormalities. For each of the abnormalities the two groups were then compared for each of the five physiologic variables using an unpaired Student's *t* test.

RESULTS

Evidence of an abnormal myocardium. Electrocardiographic: The P-R interval, when corrected for heart rate, was prolonged in six patients (five of the six also had a prolonged QT_c interval). Complete right bundle branch block developed at the time of the reaction to treatment in one patient, and partial right bundle branch block was seen in two patients. In all three, conduction was normal on the next day. The QT_c interval was prolonged beyond 0.42 second in men and 0.43 second in women in nineteen patients. The three patients in this series who died all had a substantially prolonged QT_c interval (Figure 1). In most of these nineteen patients a prolonged QT_c was seen throughout the first day; in a few, it developed after the reaction to treatment. In two patients it persisted to the fourth day and in one other patient to the third day.

In no patient was an atrial arrhythmia recorded, but ventricular ectopic beats, numerous around the reaction to treatment, were recorded in four patients (Figure 2), all of whom had a prolonged QT_c interval.

Clinical: Gallon sounds were heard in seventeen patients at some stage during the first day, but they were often dif-

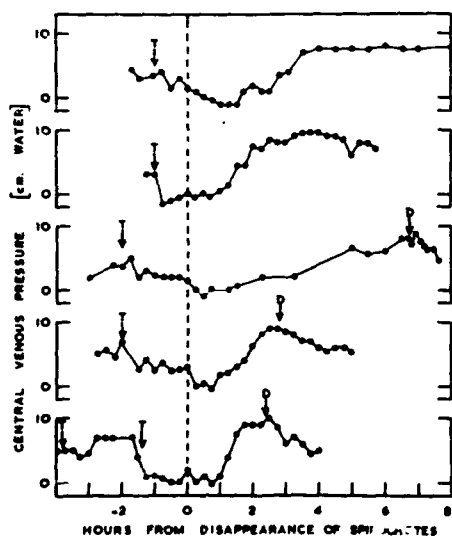


Figure 5. Central venous pressure recorded in five patients with louse-borne relapsing fever illustrates the rise in pressure after the reaction to treatment with tetracycline (T). Digoxin (D), 1.0 mg, was given by intravenous injection to three of the patients.

difficult or impossible to time because the heart rate was so rapid. In two patients a gallop rhythm was first heard six to eight hours after the reaction to treatment.

Two patients had roentgenologic evidence of cardiac enlargement. Both had pulmonary edema; in one of the two, the chest roentgenogram did not become normal until the sixth day (Figure 3).

Hemodynamic: In all but twelve patients the arterial pressure fell substantially after the reaction to treatment. Systolic pressures of around 70 mm Hg were often found at this phase. When the systolic pressure was low, the diastolic pressures were difficult to define as sounds could be heard down to zero in many patients. In the nineteen patients, however, in whom the mean arterial pressure (\bar{P}_{sa}) was recorded, the lowest levels (range 36 to 71 mm Hg) were recorded two to nine hours after the peak of the reaction (Figure 4).

The changes in central venous pressure were of two types. First, at or around the reaction to treatment in two patients it fell but rose again to its original level after four hours. Secondly, at about four hours after the reaction in six patients the central venous pressure rose abnormally and reached its peak at about the sixth hour. Digoxin, 1.0 mg by intravenous injection, was given to three of the six and in all the central venous pressure fell quickly (Figure 5). The drug was not given to the other three because at the time they were studied the significance of the high central venous pressure was not understood.

One patient whose systemic arterial pressure had fallen to 60/40 mm Hg was given an intravenous infusion of 600 ml of Periston® over forty-five minutes in an attempt to raise the arterial pressure. The result was nearly disastrous; he became distressed and breathless; his jugular venous pressure at 45 degrees rose to the angle of the mandible; a gallop rhythm and crepitations in both lung fields was heard; and

TABLE I Association Between Clinical, Electrocardiographic and Hemodynamic Signs in Fifty Patients with Louse-Borne Relapsing Fever

Data	Acute R (EKG)	Rise of \bar{P}_{sa}	Rise of CVP	Fall of \bar{P}_{sa}	Gallop Rhythm
QTc prolonged	4	1	4	9	7
Acute R (EKG)*	2	2	1	7	7
Rise of \bar{P}_{sa}		—	—	1	—
Rise of CVP†				5	3
Fall of \bar{P}_{sa}					12

* Acute R was considered to be present if two of the electrocardiographic criteria shown in Table II were found together.

† Central venous pressure.

his condition improved only when he was given digoxin and forced to sit up. Throughout all this the arterial pressure rose to 72/52 mm Hg.

Relationship between signs and measurements of myocardial damage: Table I shows the associations between signs and hemodynamic changes. It is difficult to draw any definite conclusions from this table except perhaps to state that no one clinical sign was found to be a reliable guide to any potential hemodynamic change.

Pathologic anatomy: The results of our pathologic studies are reported elsewhere [9]. Postmortem examination was performed in two of the three patients in this series who died after treatment. The postmortem findings were similar in both cases. The heart was normal in size and weight. The serosal membranes contained numerous petechial hemorrhages. Microscopic examination revealed a diffuse interstitial edema with a low grade round cell infiltrate consisting mainly of small lymphocytes, plasma cells and histiocytes. There were focal areas of myocardial degeneration

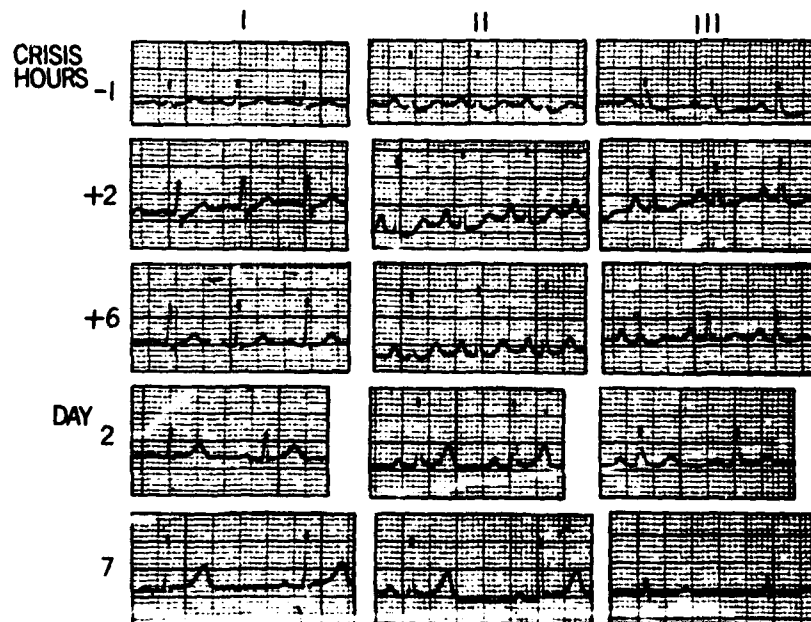


Figure 6. Electrocardiogram from a patient with louse-borne relapsing fever showing the appearance of 5 mm P wave after the reaction to treatment.

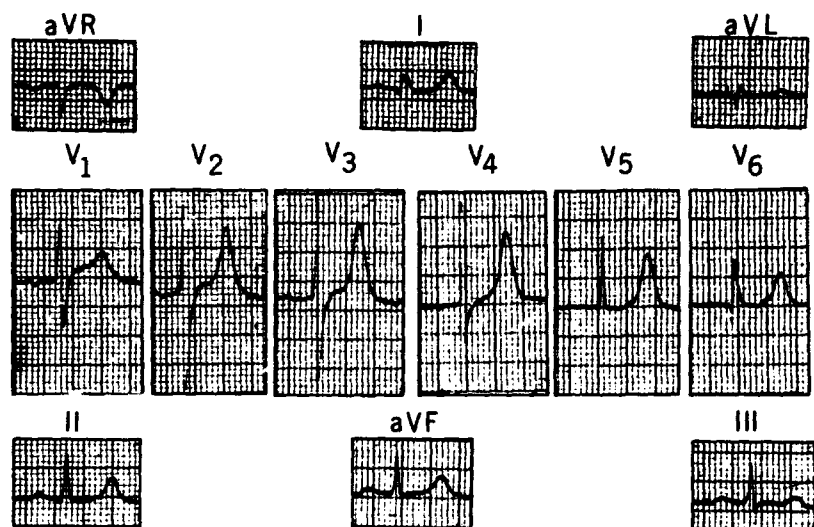


Figure 7. Electrocardiogram from a seventeen year old girl with louse-borne relapsing fever and pulmonary edema (Figure 3) illustrating change in electrical axis from +135 degrees to normal between the second and sixth days after treatment.

and interstitial hemorrhage. Cells with typical Anitschkow nuclei were present in most sections. These changes could be described collectively as interstitial myocarditis with focal myocardial necrosis.

Evidence of Acute Right Heart Changes. Electrocardiographic: In five patients a tall peaked P wave of 3 mm or more was seen (Figure 6); in one patient the P wave measured 5 mm. The electrical axis changed in seventeen patients. At or soon after the crisis the mean QRS axis was to the right (>90 degrees) compared with the mean QRS axis before or after the reaction to treatment. One patient who had pulmonary edema had an axis of +135 degrees on the day after treatment, and this returned gradually to normal (Figure 7).

A secondary R wave of 2 mm or more was seen in lead aVR in thirteen patients; in those in whom follow-up cardiograms were taken it became less or disappeared.

Deep S waves in the left precordial leads, V_1 and V_6 , were seen in thirteen patients. These became smaller or disappeared during the first week in the patients who were followed up.

Widespread changes in the T waves were seen often. Inverted T waves over the right ventricle (leads V_1 through V_3) have been considered as possible evidence of acute right heart change. Such T wave changes were found on the day of treatment in five patients and on the day after treatment in one. Two of the five no longer showed inverted T waves on the second day.

Hemodynamic: A fall in \bar{P}_{ra} during the rigors, with a subsequent rise above the pretreatment level, was recorded in all five of the patients in whom repeated measurements were possible (Figure 8). \bar{P}_{ra} reached its maximum (range 18 to 34 mm Hg) two and a quarter to three and three-quarter hours after the rigors. No gallop rhythm was heard in any of these five patients, and in all of them \bar{P}_{ra} had begun to fall towards the pretreatment level four hours after the peak of the reaction.

The three patients whose \bar{P}_{ra} rose highest all had an ab-

normal electrocardiogram. In the one whose \bar{P}_{ra} rose to 34 mm Hg two and a half hours after the rigors, the P wave increased to 3 mm between two and six hours after the rigors. In a second, there was a shift of electrical axis and clockwise rotation; and in the third, inverted T waves appeared in the anterior chest leads, particularly over the right ventricle, after the peak of the reaction, but these had become nearly upright by the next morning.

Association between electrocardiographic and hemodynamic data: The relationships are shown in Table II. Again there is no constant pattern of relationship between the different variables.

Relationship Between Electrocardiographic Changes and Physiologic Disturbances. Comparisons of values for T_{ra} , heart rate, Pa_{CO_2} , Pa_{O_2} , and H^+a in patients with and without each of three electrocardiographic abnormalities (abnormal T waves, S-T segment depression and QT_c prolongation) before treatment during the rigors achieved levels of statistical significance greater than 10 per cent (i.e., $p < 0.1$) in only two instances: before treatment five patients with prolonged QT_c intervals had a mean H^+a of 43.3 nM/L (standard deviation [S.D.] ± 5.1) whereas twelve patients with normal QT_c intervals had a mean H^+a of 39.7 nM/L (S.D. ± 2.2) $p = 0.054$ for 15 degrees of freedom; during the rigors fourteen patients with abnormal T waves had a mean Pa_{CO_2} of 25.2 mm Hg (S.D. ± 2.2) whereas three patients with normal T waves had a mean Pa_{CO_2} of 31.2 mm Hg (S.D. ± 6.0) $p = 0.007$ for 15 degrees of freedom.

None of the patients in this series showed abnormalities of serum electrolytes which could have explained their abnormal electrocardiogram.

COMMENTS

As there are such distinct changes in the myocardium of patients who die with relapsing fever, it is perhaps not surprising that there is substantial electrocardiographic evidence of this "myocarditis." We have previously mentioned the pro-

longed QT_c in the electrocardiogram [6]; our present study amply confirms this. Similar changes have been described in leptospirosis [10].

It is relevant to note that all the patients who died had a prolonged QT_c, and we suggest that the interval should be measured in every patient with louse-borne relapsing fever, both before and during treatment. The S-T segments and T waves were superficially normal in six of our patients with an alarmingly long QT_c, so one could easily be deceived by these cardiograms of infection. But we have not been able to find any consistent association between a prolonged QT_c and conventional clinical signs of myocardial damage; of the two patients with roentgenologic pulmonary edema, only one had an abnormal QT_c; gallop sounds, also, were an unreliable sign and were, for example, absent in four patients and present in only three of those in group II with a prolonged QT_c. There was no evidence of persisting myocarditis in the patients who survived. The myocarditis could be incriminated as an important cause of the low systemic arterial pressure which was almost invariable about four hours after the reaction to treatment.

The low values for total systemic vascular resistance obtained by Warrell et al. [8] are probably explained by renal and splanchnic vasodilatation caused by pyrogen. This mechanism is chiefly responsible for the low arterial pressure, but myocardial damage and other factors, such as extracellular fluid volume depletion due to fever, may contribute and may precipitate irretrievable hypotension. These patients must maintain a high cardiac output, usually about 8L/minute, throughout the phase of systemic vasodilatation in order to preserve a reasonable blood pressure [8].

Raised body temperature and a variety of electrolyte and acid-base disturbances have been associated with electrocardiographic abnormalities, but, as fever is so physiologically complex, it is difficult to attribute particular electrocardiographic abnormalities to changes in any single variable. Freedberg et al. [11] described flattening or inversion of the T wave and S-T segment depression in subjects made febrile by injection of typhoid vaccine, but these changes may have been due to the respiratory alkalosis and tachycardia which accompany fever rather than to a distinct effect of

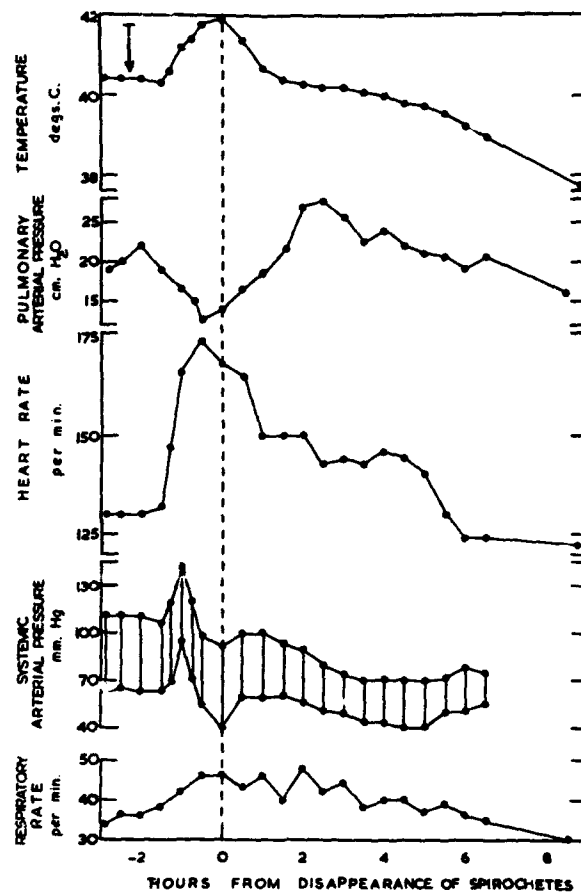


Figure 3. Rectal temperature, pulmonary artery mean pressure, heart rate, systemic arterial pressure (systolic/diastolic) and respiratory rate in a patient with relapsing fever given tetracycline (T) illustrating the rise in pulmonary artery pressure during the flush phase of the febrile reaction to treatment.

TABLE II Association Between Electrocardiographic and Hemodynamic Data in Fifty Patients with Louse-Borne Relapsing Fever

Data	Axis to Right	S Waves in Leads V ₁ - V ₄	R in Lead aVR	T Inverted Leads V ₁ - V ₄	Rise of P _{ra} *
P wave	3	1	1	1	1
Axis to right		6	3	2	2
S waves in leads V ₁ - V ₄			5	2	1
R in lead aVR				—	—
T inverted in Leads V ₁ - V ₄					1

* Measurements of P_{ra} made in only five patients.

elevation of temperature on the myocardium. In seventeen of our patients with relapsing fever we have tested for statistical significance the correlation between the three most common electrocardiographic abnormalities (prolonged QT_c, T wave abnormalities and S-T depression) and five important physiologic variables (PaO₂, PaCO₂, H⁺a, T_a and heart rate). The only statistically significant correlations were between prolonged QT_c and a relatively low blood pH before treatment, and between T wave abnormalities and hypocapnia during the chill phase of the febrile reaction. A cause and effect relationship between the physiologic and electrocardiographic abnormality is by no means established. For example, the combination of low PaCO₂ and normal or high H⁺a in the patients with prolonged QT_c implies that a metabolic acidosis was present in addition to respiratory alkalosis [8]. Prolonged QT_c provided evidence of myocardial damage which, by impairing cardiac output, may have caused the

acidosis. The literature is full of unfounded correlations of this sort. It seems more likely that the observed changes reflect the interaction of many different physiologic changes on the myocardium.

The hemodynamic evidence of a raised P_{A} after the reaction to treatment and the electrocardiographic evidence of right-sided changes are very interesting. The electrocardiographic changes are not as marked as are seen in some cases of acute cor pulmonale, but the shift of electrical axis, the clockwise rotation, the R wave in lead aVR, the P pulmonale and the inverted T waves over the right ventricle are still good evidence of acute cor pulmonale. The T wave changes in the right precordial leads are less reliable, however, as they have been found often in healthy normal young Ethiopians [12] and are well known in other African countries as a normal electrocardiographic variant [13]. Clinically, we have not relied on the difficult sign of an accentuated pulmonary closure sound because of the ease of observer error, although some of us recorded this sign during our prolonged clinical studies.

There are four possible explanations for this transient "cor pulmonale." First, in one patient the acute right-sided changes, most obvious when she had severe pulmonary edema, disappeared as her pulmonary edema cleared. A possible but not wholly satisfactory hypothesis is that left ventricular myocardial damage leads to a high end-diastolic pressure and the inevitable pulmonary venous and arterial hypertension. In rare cases frank pulmonary edema occurs; in most others the increase in pulmonary arterial pressure is sufficient to affect the electrocardiogram transiently, but no more. Secondly, an entirely speculative but attractive hypothesis is that microemboli block the pulmonary vascular bed. These microemboli might consist of clumped spirochetes which can be seen in the blood films about the time spirochetes begin to disappear before the reaction to treatment, or they might be fibrin particles formed by disseminated intravascular coagulation [14]. There is no evidence that platelets are destroyed during the reaction to treatment [14], and so we cannot postulate that 5-hydroxytryptamine, for example, liberated from these cells, causes the pulmonary hypertension. Thirdly, it is possible that endotoxin released by disintegrating spirochetes may increase the pulmonary artery pressure. Endotoxin is present in high concentrations

in the blood of patients with louse-borne relapsing fever when spirochetes disappear [15] and is known to produce changes in pulmonary artery pressure similar to those observed in our patients [16,17]. Fourthly, the high altitude of Addis Ababa (7,500 feet) and the respiratory disturbances observed in our patients raise the possibility of acute high altitude cor pulmonale. There was, however, no fall in Pa_{O_2} or calculated alveolar P_{O_2} throughout the reaction, and the inhalation of 100 per cent oxygen did not prevent a characteristic increase in pulmonary artery pressure after the chill in one patient [8]. High altitude pulmonary hypertension has been observed during exercise in residents at altitudes of 8,000 feet and above [18], and since the physiologic changes of high fever resemble those of exercise [19] it remains possible that this was the mechanism of our patients' right ventricular strain.

The many speculative hypotheses which we have proposed to explain our findings of cardiovascular changes in relapsing fever show that it is impossible to define the separate effects of fever, endotoxin and myocardial damage. Whatever these individual effects may be, it is certain that the myocardium is often seriously affected and that profound hemodynamic changes occur in both the pulmonary and systemic circulations. Ideally, treatment should include nursing the patient lying flat to maintain systemic arterial pressure, a continuous infusion of isotonic saline solution to maintain the extracellular fluid volume, monitoring the electrocardiogram for runs of ventricular ectopic beats, giving 100 per cent oxygen to prevent lactic acidosis [8], digoxin to support the myocardium and keeping the patient at rest in bed until the QT_c in the electrocardiogram has returned to normal.

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